FINAL REPORT

Project B-508

DIELECTRIC MEASUREMENTS OF NORMAL AND NEOPLASTIC TISSUE

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INTRODUCTION

The purpose of this research program was to investigate techniques for utilizing differences in the measured dielectric properties of normal and neoplastic human tissues to select, on an *a priori* basis, frequencies for electromagnetic (EM) hyperthermia treatment which result in maximum differential power absorption and therefore, maximum differential heating of tumors with respect to normal tissue. Ultimately, the basic dielectric data and predictive analyses will make possible EM hyperthermia treatment planning in which the optimal frequencies, applicators, and power levels can be established before treatment. The specific aims of this research were the following:

1. Perform *in-situ* dielectric property measurements on normal and neoplastic tissues in animal model systems and determine the differences between the dielectric characteristics of tumor tissues and normal host tissues.

2. Perform measurements of normal skin tissue and surface lesions in humans over a wide frequency range.

3. Quantitate effects of temperature, tumor volume, and morphology on measured dielectric properties of specific tumor types.

4. Determine and assess the complexities involved in analytically determining the spatial distribution of absorbed EM energy in tissues having geometrical configurations, depths, and volumes encountered clinically and in determining the resultant induced heating patterns.

5. Examine the effects of hyperthermia administration on the dielectric properties of solid tumors.

6. Utilize measured human and animal dielectric property data for determining relative differences in electromagnetic power absorption by tumors and normal tissues as a function of frequency.

Quantitation of the *in-vivo* dielectric properties of normal and neoplastic tissues was a primary objective of this research. These properties are important because they determine the manner and extent to which tissues interact with any applied EM energy. That is, phenomena such as (1) the phase delay and attenuation experienced by an EM wave propagating through biological tissue, (2) the coupling and/or reflection of incident EM energy with a biological body, and (3) the absorption of EM energy by tissue and its subsequent dissipation as heat, are determined by the tissue's dielectric properties. Further, when combined with a suitable analytical technique, accurate dielectric property data can be used to determine these phenomena on an *a priori* basis.

Because of the significance of tissue dielectric property data, a large number of investigators have used conventional techniques to measure the dielectric properties of various tissues [1-6]. However, these have primarily

been in-vitro measurements on excised tissue samples and include only cursory data for neoplastic tissues. The absence of reliable in-situ dielectric property data for living normal and neoplastic tissue can be largely attributed to the lack of a suitable measurement technique. This situation was remedied by our development of a new technique specifically designed for measuring the dielectric properties of living tissue in-situ over a wide frequency range [7-9]. This new technique is ideal for measurements on small or irregularly shaped samples such as tumors and has been successfully utilized in several other research programs [11-12].

A. Dielectric Properties -- Definition and Significance

A wide variety of parameters can be used to quantitate a material's dielectric properties. These properties are usually expressed as the complex permittivity $\varepsilon^*=\varepsilon'-j\varepsilon''$. In this report, the dielectric parameters are defined as follows:

- Relative dielectric constant (symbolized as K' and equal to $\varepsilon'/\varepsilon_o$, where ε_o is the permittivity of free space),
- Relative loss factor (symbolized as K"),
- Loss tangent (symbolized as $\tan\delta$ and equal to the ratio K"/K'), and
- Electrical conductivity (symbolized as σ and equal to the product $\omega\,\varepsilon_o\,K'$ where $\omega = 2\pi f$, and f is the frequency).

A material's dielectric properties are essentially a measure of its ability to interact with EM energy. Since this interaction results from the presence of components within the material that can be affected by the electric and magnetic forces generated by the EM energy, a material's dielectric properties are a direct consequence of its composition and structure. In non-magnetic materials such as tissues, an EM field will primarily act upon components within the material that possess either a net electrical charge or an electric dipole moment [13]. The motion imparted in these components results in an electric current flow within the material. In tissue, components possessing a net electrical charge are mainly ions (e.g. Na^+, Cl^-, K^+, Ca^{+2}, etc.,). Polar molecules (such as water) are the main source of electric dipole moments in tissues. Protein structures, muscle and fat bulk, etc., are additional sources of electric dipole moments [1]. Because the dielectric properties of a tissue are determined by such a wide variety of components, these properties exhibit significant variations as a function of parameters such as frequency, temperature, and tissue type and vascularization.

B. Previous Tissue Dielectric Property Investigations

Numerous investigations of tissue dielectric properties have been conducted by Schwan [1,14] utilizing short-circuited transmission line and bridge techniques. By combining these data with the low frequency tissue data measured by Rajewsky [2] and Osswald [3], and with Herrick's microwave frequency data, Schwan was able to establish a useful base of in-vitro dielectric

data for various normal tissues over an extremely wide frequency range [1]. Examination of those data reveals the existence of two dispersion regions in tissue dielectric properties in the frequency range from 3 MHz to 30 GHz. These dispersion regions are important because they are characterized by significant variations in dielectric property values as a function of frequency. Schwan entitled these regions the dispersion regions and related the dispersion phenomena to various tissue components. The β dispersion, which occurs at approximately 1-10 MHz, is due to the presence of subcellular structures and proteins. An additional dispersion, termed the α dispersion, exists over approximately the 0.5-4 GHz frequency range and is much smaller in magnitude than the other dispersion. The α dispersion results from protein-bound water and partial rotation of polar subgroups. As the EM frequency is increased, the membranes are effectively short-circuited and at microwave frequencies, the tissue dielectric properties are largely influenced by the tissue water and electrolyte content. In high-water-content tissues, the dispersion occurs at approximately 20 GHz, depending upon tissue temperature.

Investigations of tissue dielectric properties were also conducted by Cook [5] and by Roberts and Cook [6]. Cook employed a short-circuited coaxial transmission line to obtain dielectric property data for muscle, skin, and fatty tissue over a limited frequency range (1.8 to 5.0 GHz). Roberts and Cook investigated the dielectric properties of blood, muscle, and fatty tissue in the and dispersion regions (aproximately 1.0-30 GHz). Their investigations verified the dispersion phenomena exhibited by the dielectric properties of biological tissues in this frequency range. Roberts and Cook [6] also found that by including a term to account for ionic conductivity and using the relaxation times of pure water, Debye dispersion equations could be utilized to describe the dielectric properties of muscle and blood over the UHF/microwave frequency range. This fact verified that the dielectric properties of these tissues in this frequency range are determined primarily by water and electrolyte content, with proteins and other constituent molecules also producing a minor contribution.

Several investigations have been directed at obtaining and compiling in-vitro dielectric property data for various normal animal and human tissues. These investigations include the surveys by Tinga and Nelson [15], Johnson and Guy [16], Geddes and Baker [17] and Schwan and Foster [18]. In the well known Johnson and Guy investigation, tissues were classified into two categories: (1) muscle, skin, and other tissues with "high water content" and (2) fat, bone, and other tissues with "low water content." The results of the Johnson-Guy survey are of particular interest and utility because data are presented at frequencies pertinent to industrial and medical users of EM radiating equipment (e.g., 13.56, 27.12, 918 and 2450 MHz). However, by classifying tissues into only two categories, no accounting is made of individual tissue types or physiological characteristics. These previous investigations have resulted in data that have proven to be extremely useful to studies involving the interaction of biological tissues with EM energy. However, these results were obtained from in-vitro measurements that do not

reflect the actual physiological conditions of living tissues and none of these data represent measurements of neoplastic tissues.

Efforts in the area of in-situ permittivity measurements at RF and microwave frequencies began a decade ago with preliminary work performed by Magin and Burns [20]. Their technique utilized a monopole probe that behaved electrically as a short antenna which could be inserted into tissue. The frequency range of their technique was limited, but preliminary dielectric property data for tissues in mice, rats, and dogs were measured. More recently, Toler and Seals [11] improved the accuracy of the monopole antenna approach from 10-100 MHz. Hahn [21] modified the instrumentation and probe configuration and performed dielectric property measurements on various animal tissues. However, the frequency range of this technique was only 3-100 MHz and no corrections for systemic errors was employed. A second in-situ dielectric property technique utilizing a probe described as an "open transmission line resonator" has also been recently investigated [22]. This technique utilizes a section of open-ended coaxial cable that is placed in contact with a sample of the material being measured. Because of instrumentation problems, this technique was accurate over only a limited frequency range from 1.0-4.0 GHz. Joines, Tanabe and U [23] utilized this technique to perform preliminary dielectric property measurements on normal and neoplastic tissues in human subjects. Their limited results indicated possible differences in the dielectric properties of normal and neoplastic tissues. Guy [24] developed and used a "four-electrode" technique to measure the electrical conductivity of normal canine muscle tissue.

The most versatile and broadband in-situ measurement technique is the dielectric measurement probe developed at Georgia Tech by Burdette, et. al., [7-10, 12]. The operational frequency range of the probe extends from 1 MHz to 10 GHz. Under this research program, the flexibility of technique and data acquisition speed were greatly increased by automating the measurement process under microcomputer control. The accuracy of the technique over this frequency range has been verified by measurements of reference materials such as water, methanol, ethylene glycol, etc., which have well documented dielectric properties. The technique has been used successfully to perform dielectric property measurements on a variety of living animal tissues under in-situ conditions and on samples of muscle equivalent phantom modeling materials [11, 12, 25-27]. The probe's theoretical basis and measurement instrumentation are discussed in detail in Reference 9.

The remainder of this report summarizes the research performed under NCI Grant No. R01-CA22771 during the period from April 1, 1978 through August 31, 1983.

RESULTS OF

RESEARCH PERFORMED

As stated in the Introduction, the primary goal of this research program was to determine if differences exist between the dielectric characteristics of normal and neoplastic tissues and to provide basic data for a number of normal and cancerous tissues over a wide range of frequencies.

A. Work Performed During Grant Years 01 and 02

The major goals for the first two years of the program involved improving the accuracy and repeatability of probe measurements, decreasing the time required for data acquisition and processing to the extent that data would be processed on a real-time basis, performing in-vivo dielectric measurements of several mice tumor lines and rat sarcoma, and performing initial in-situ measurements of superficial lesions in humans.

1. System/Protocol Development

In the area of further measurement technique development, several aspects were addressed. These aspects included probe fabrication, proper positioning of the subject during measurement procedures, increased flexibility in probe positioning, design and fabrication of an environmentally-controlled chamber, and implementation of a data acquisition-/data processing system.

It was determined that factors such as imperfect attachment of connectors and deformities in the semi-rigid coaxial cable used to fabricate the in-vivo probes resulted in measurement errors and reduced the useful frequency range of the probe. Problems of the above nature were minimized by using assembly tools expressly designed for precision attachments of connectors to semi-rigid coaxial cable and by cutting and facing off the probes using a jeweler's lathe. Using these fabrication techniques, it was possible to repeatedly fabricate probes yielding consistent and accurate reslts. The probes were also gold-plated before assembly which minimized any possible chemical reaction between the tissue being measured and the probe itself and helped eliminate the effects of electrode polarization at lower frequencies (1-40 MHz).

A gear assembly consisting of a jack stand sitting on a movable platform was configured to permit proper positioning of the subject with respect to the fixed measurement probe. In the case of mice and rats with implanted subcutaneous tumors, the test animals were positioned horizontally beneath the probe, and the jack stand was used to vertically position the animal to bring the probe in proper contact with the tumor. Accurate positioning was

necessary because each set of data was repeated four to eight times. In this manner, the repeatability of the measurements could be investigated, and any changes in measured results due to changes in probe contact pressure could be readily evaluated.

A more flexible procedure for probe positioning was necessary to perform in-situ- dielectric measurements on animals larger than the mice or rats which could be positioned beneath a fixed measurement probe. Both semi-rigid and flexible coaxial cables attached to the in-vivo measurement probe were evaluated as a means for achieving the required flexibility. The technical requirements of a suitable cable were (1) a suitable length for positioning the probe on a large experimental animal or human subject while permitting convenient location of the network analyzer used in conjunction with the probe (see Figure 1), (2) introduction of minimal phase variations due to cable movement, (3) low attenuation, and (4) the ability to withstand sterilization. Following examination of cables from nearly a dozen manufacturers, Gore-Tex flexible cable (manufactured by W. L. Gore and Associates) was selected. This cable was found to be adequately flexible, having a specified phase variation with flexure of only two degrees at 10 GHz when wrapped around a 3-inch mandrel, and met all other electrical and mechanical requirements. Also, the Gore-Tex cable may be gas sterilized without any deterioration in performance.

An environmentally-controlled chamber, in which temperature, humidity, and air flow were controlled independently, was designed and fabricated for use during mice tumor measurements. Dry heat temperature was controlled via a temperature adjustable heating coil located directly in front of a variable-speed blower which in turn controlled the air flow through the chamber. Humidity was regulated by controlled injection of heated water vapor into the air stream. The environment within the chamber could be maintained at levels which minimized changes in moisture content and temperature of the implanted tumor without causing the animal to become hyperthermic. Under high humidity conditions, the animal was placed on a respirator.

A microcomputer-based data acquisition/data processing system was also developed. Implementation of the automated data acquisition and processing system was of key importance to the laboratory measurements performed under this grant because of the enormous volume of tumor and normal tissue dielectric data which had to be processed and reduced. Further, semi-automating the data acquisition process decreased the time required to acquire the data and resulted in accuracy improvements by significantly reducing human involvement in the tedious data collection process and by incorporating a model for the reduciton of systemic measurement errors associated with network analyzer measurement systems [9]. The present semi-automated data acquisition/data processing system is shown in Figure 1. The key components in the semi-automated measurement system are a Hewlett Packard network analyzer and a desktop computer. Other hardware items include a printer and printer interface an IEEE Standard 488-1975 compatible bus which interfaces to a Hewlett-Packard digital frequency counter and sweep frequency generator, and a parallel interface to a multiplexer/12-bit analog-to-digital

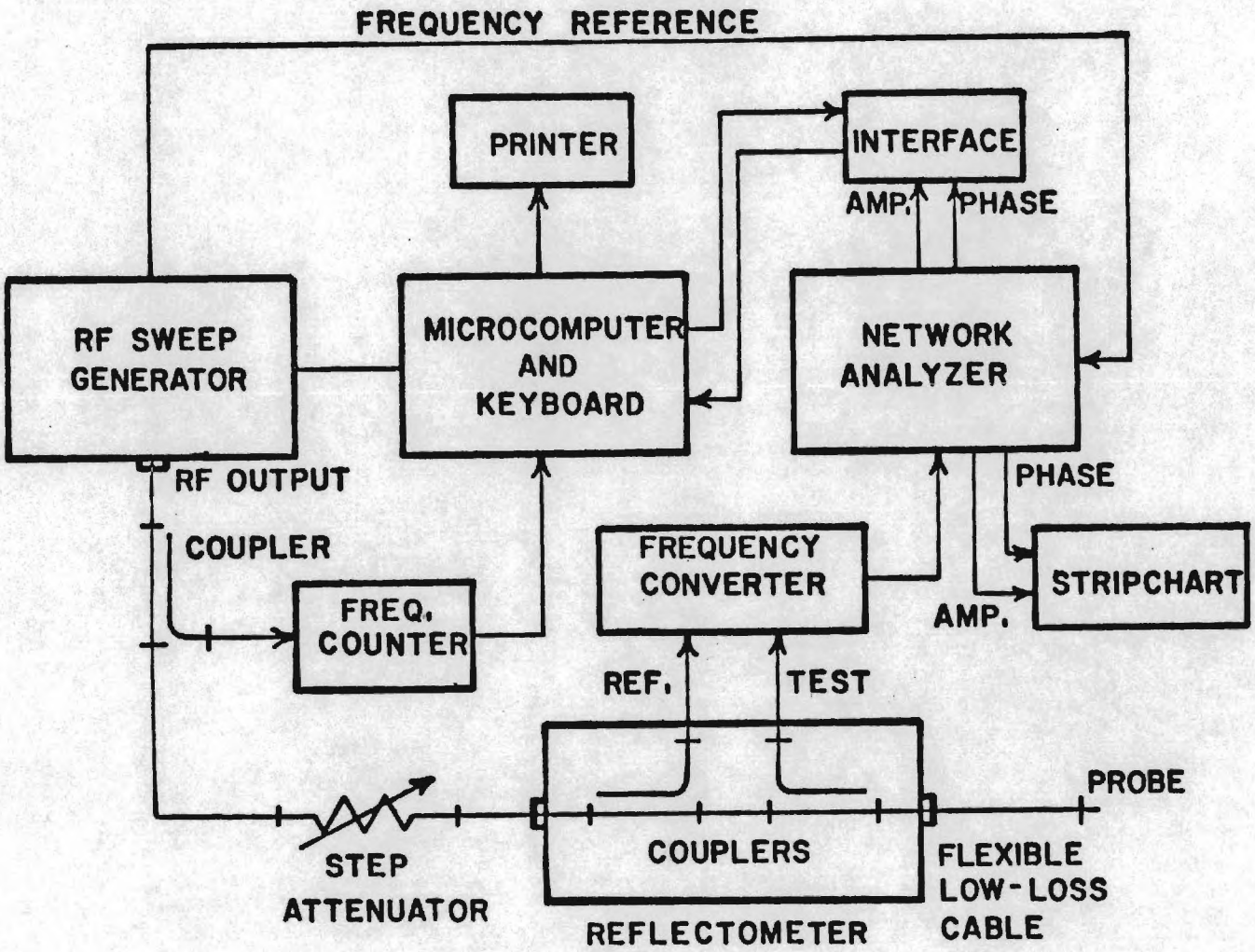


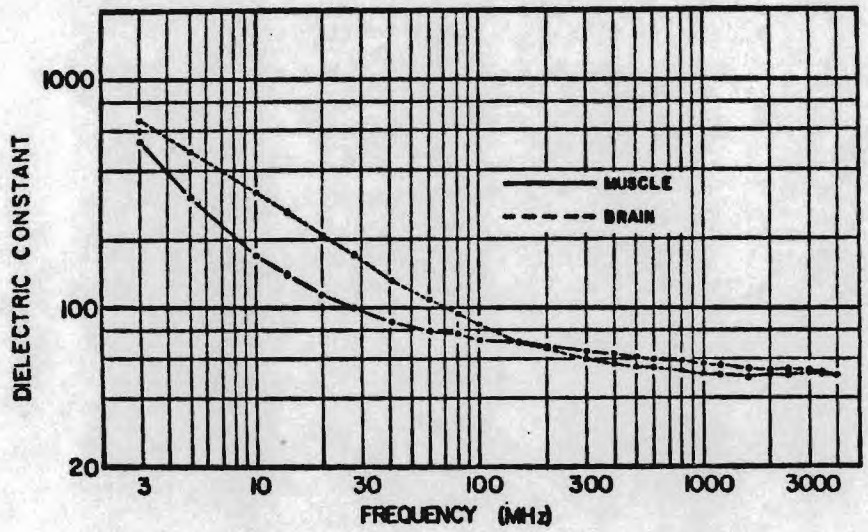
Figure 1. Block diagram of the semi-automated data acquisition/data processing system used for measuring in-situ dielectric properties of living tissues.

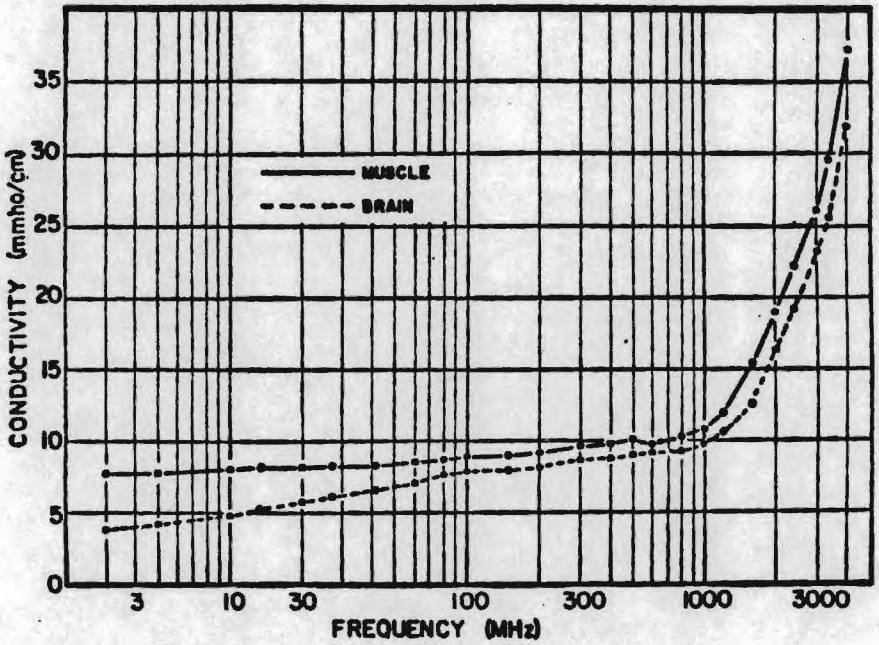
converter (MUX/AD). This data acquisition system permits both rapid, accurate data collection and correction of the inherent directivity, source match, and frequency tracking systemic measurement errors. The system automatically collects measured reflection coefficient data from the probe, processes these data, and outputs corrected dielectric property information.

2. Results of In-Situ Dielectric Property Measurements

During the first two grant years, a large number of in-situ dielectric property measurements were performed on a variety of normal and neoplastic tissues in mice and rats. A limited number of in-situ measurements were also performed on human subject. These measurements were performed primarily to validate the following hypotheses: (1) a difference exists in the dielectric characteristics of normal and neoplastic tissues, (2) differences in dielectric characteristics exist among the different types of neoplastic tissues, and (3) these differences in dielectric characteristics can be used to aid in the selection of suitable frequencies for differentially heating and destroying neoplastic tissues. Each of these hypotheses was validated by the results of in-situ dielectric property measurements performed over the 3 MHz - 4 GHz frequency range. At frequencies of approximately 4 GHz and above, the useful penetration depth of EM energy is very small. In fact, these frequencies (greater than 4 GHz) can be used for heating small surface lesions because of the very small depth of EM energy penetration into the tissue (less than 0.5 cm). Therefore, any differences in the dielectric properties of normal and neoplastic tissues at the higher microwave frequencies would provide little, if any advantage in the treatment of surface lesions, and essentially no advantage in EM hyperthermia treatment of deep-seated tumors. The only case for which differential dielectric information would possibly be useful at frequencies of approximately 4 GHz or higher would be where the EM energy is deposited in the tumor (within a small volume) using a needle-like probe or in radiometric detection of lesions. Results of the measurements performed under this grant are discussed in the following paragraphs.

The rat tissues measured included normal muscle and brain and one tumor line (syngeneic methylcholanthrene induced sarcoma) [27]. The measurements were performed on anesthesized animals and extended over the frequency range from 3 MHz - 4 GHz. Six to ten specimens were measured for each of the rat tissue types with each specimen being measured four to eight times. The measurements on the rat muscle tissues were performed by placing the probe on surgically exposed thigh muscle of the rat. Surgery for the muscle measurements consisted of a 1-cm long scapel incision through the skin and subcutaneous tissues covering the thigh muscle. The brain measurements were performed with the probe placed either on the exposed pial surface or directly upon the gray matter. A 2-cm long scapel incision was made to provide access to the upper skull, followed by the boring of a small hole ($\approx$ 3mm diameter) through the skull to expose the brain. Excess dural and bone fragments and excess fluids were removed prior to the dielectric property measurements. For the rat tumor measurements, a 1 cm x 1 cm skin flap was cut and subcutaneous tissue covering the tumor was removed to expose the tumor surface. The tumor measurements were performed on either the more vascularized tumor surface or





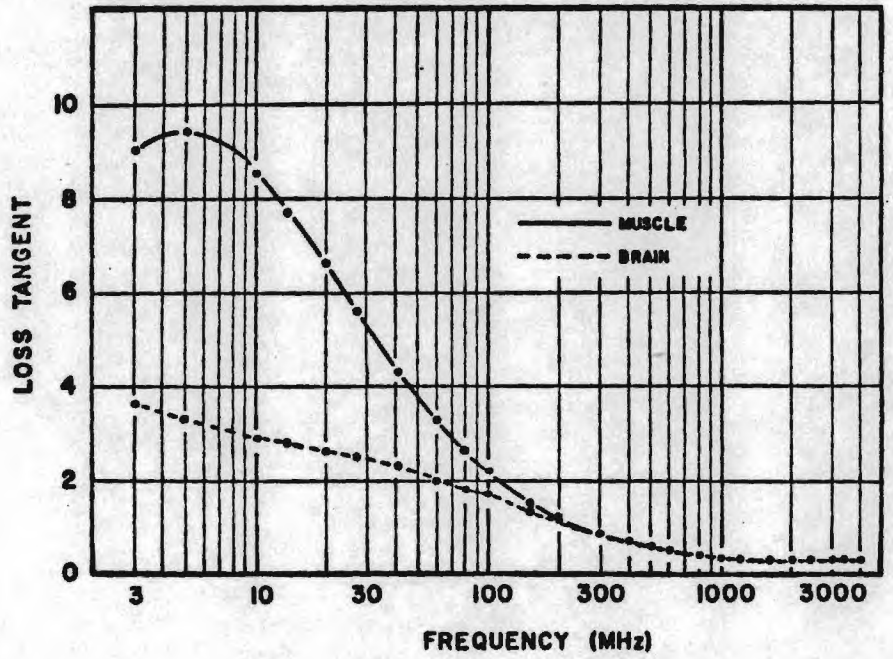


Figure 2. In-situ dielectric properties of normal rat muscle and rat brain tissues.

Temperatures during measurements:

Muscle	(Rectal)	35°C ± 2°C
	(Site)	29°C ± 2°C
Brain	(Rectal)	33°C ± 5°C
	(Site)	34°C ± 2°C

Maximum SEM values:

Dielectric Constant	6% of mean value
Conductivity	6% of mean value
Loss Tangent	8% of mean value

on subsurface (2-3 mm deep) tumor tissue.

A number of observations result from examination of the rat tissue dielectric property measurements. Normal muscle and brain tissues are classified by several investigators into a single category: tissues with "high-water content", assumed to have very similar dielectric properties [16]. However, examination of Figure 2 shows that significant differences exist in the dielectric properties of these two tissues, particularly at lower frequencies. As a numerical example, at 5 MHz, the relative dielectric constant of rat muscle is 62 percent of that of rat brain, the loss tangent of rat brain is 35 percent of that of rat muscle and the electrical conductivity of rat brain is 54 percent of that of rat muscle. Differences of this magnitude would significantly impact the accuracy of any analytical studies performed to compute EM energy absorption and of any tissue heating due to an applied EM field. Our studies have shown that, for complex structures like the brain, dielectric properties can vary significantly as a function of parameters such as tissue type (e.g., white and gray matter of the brain as in Figure 8) and degree of vascularization [29,30]. These examples clearly demonstrate the inadequacy of classifying tissues into just two categories such as "high-water content" and "low-water content" tissues. It was also apparent that accurate in-vivo dielectric property data are needed for a variety of other normal tissues to insure that any measured tumor dielectric property data can be evaluated with respect to that of the appropriate host tissue.

The rat sarcoma measurements were performed on the more vascularized tumor surface and on tissue approximately 2-3 mm beneath the tumor surface. The results of the surface and sub-surface tumor measurements are shown in Figure 3. These data indicate that the dielectric properties of the surface and sub-surface tumor tissue are similar, but that differences of 10-15 percent exist at frequencies below 100 MHz. These results appear consistent with the somewhat higher degree of vascularization present on the tumor surface. Characterization of dielectric properties measured at the tumor core and further studies to quantitate the effects of tumor volume/age and phenomena such as the onset of tumor necrosis on dielectric properties are also needed.

The results of the rat sarcoma measurements are compared to rat muscle data in Figure 4. Standard-Error-of-the-Mean (SEM) values were computed at each frequency point and these are included on the graph. Cases in which the SEM was too small to plot are shown as a single point. Because the dielectric properties of the rat muscle and tumor tissues tended to converge at higher frequencies, the data as plotted in Figure 4 extend only over the frequency range from 3-300 MHz. The results indicate significant differences in the dielectric properties of the two tissues at frequencies below 40 MHz. For example, at 3 MHz, the relative dielectric constant of the rat muscle is only 52 percent of that of rat tumor, the loss tangent of rat tumor is only 33 percent of that of rat muscle, and the electrical conductivity of rat tumor is only 63 percent of that of rat muscle. Conversely, at higher frequencies, the dielectric properties of the rat muscle and tumor tissues are nearly

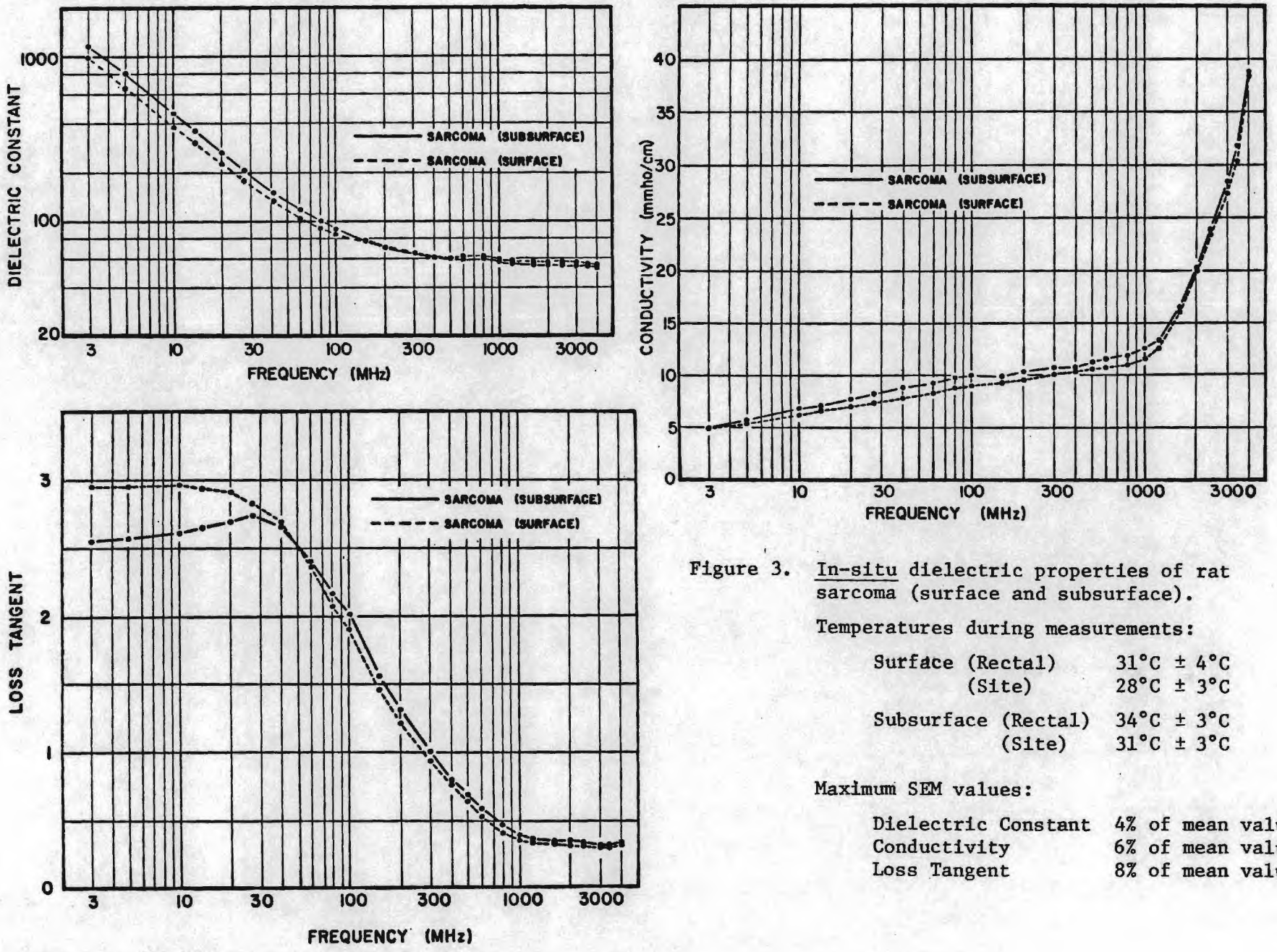


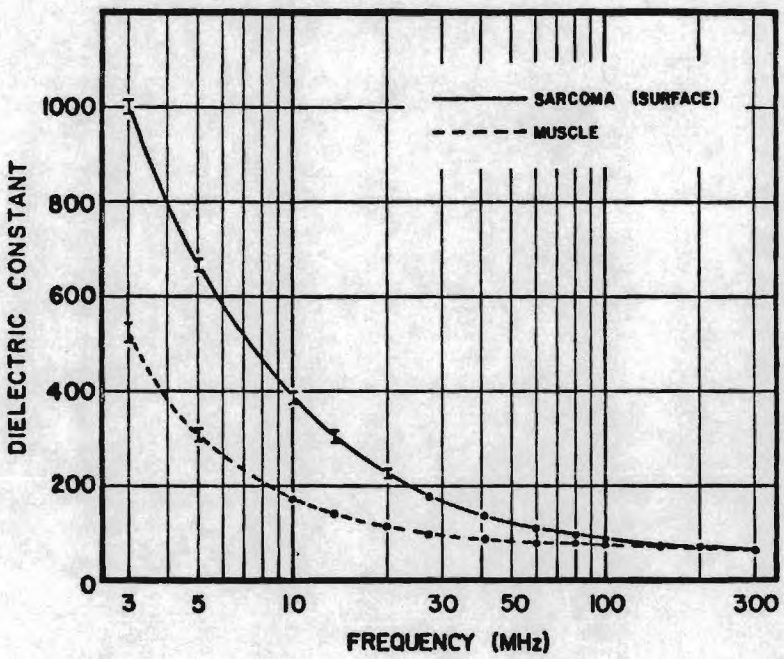
Figure 3. In-situ dielectric properties of rat sarcoma (surface and subsurface).

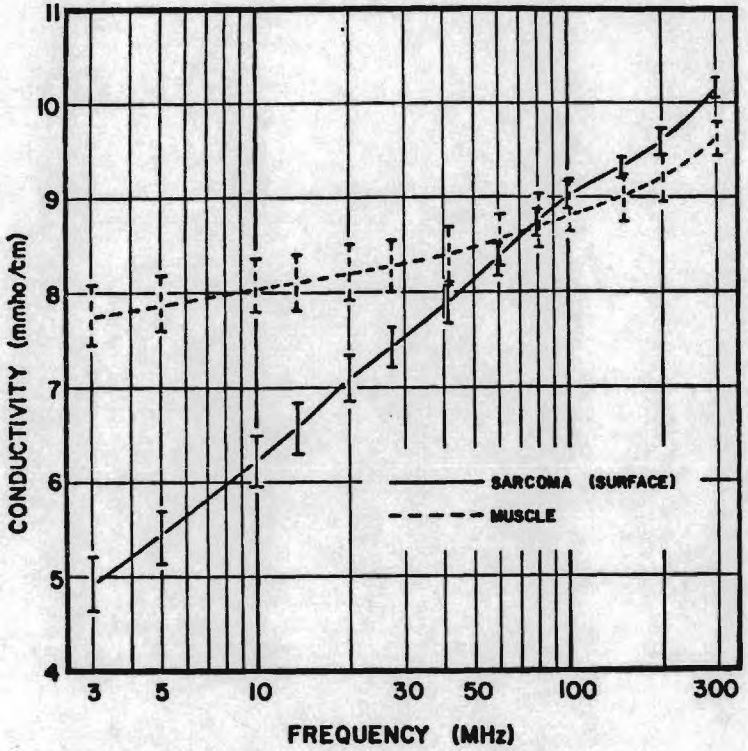
Temperatures during measurements:

Surface (Rectal)	31°C ± 4°C
(Site)	28°C ± 3°C
Subsurface (Rectal)	34°C ± 3°C
(Site)	31°C ± 3°C

Maximum SEM values:

Dielectric Constant	4% of mean value
Conductivity	6% of mean value
Loss Tangent	8% of mean value





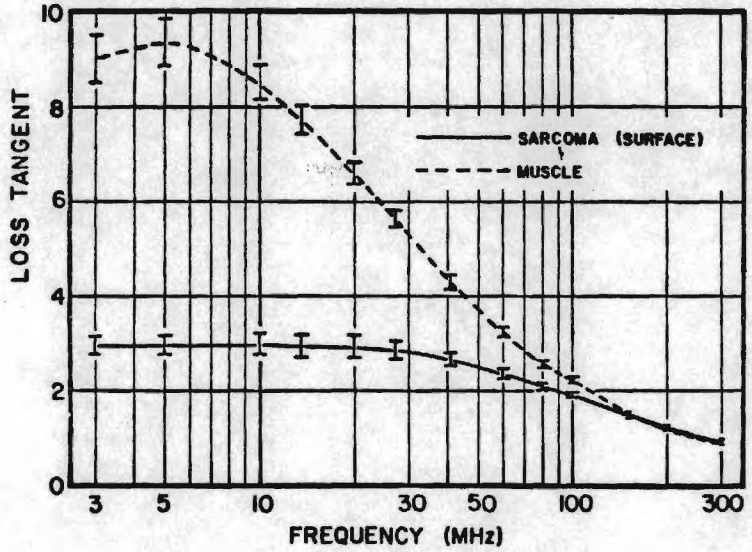


Figure 4. In-situ dielectric properties of normal rat muscle and rat sarcoma (surface).

Temperature during measurements:

Muscle (Rectal)	35°C ± 2°C
(Site)	29°C ± 2°C
Sarcoma (Rectal)	31°C ± 4°C
(Site)	28°C ± 3°C

Maximum SEM values:

Dielectric Constant	4% of mean value
Conductivity	6% of mean value
Loss Tangent	8% of mean value

identical. It is apparent that an effort to utilize EM hyperthermia to treat this sarcoma would greatly benefit from knowledge of the dielectric properties of the tumor and normal tissues. The greatest differential EM heating could be achieved at frequencies below 30 MHz. The method of EM heating (resistive, inductive, or dielectric) and type of EM energy applicator could also be selected with respect to the relationship of the various dielectric properties of the normal and malignant tissues. Because of the significant lower tumor conductivity in the above case, resistive heating of the sarcoma at relatively low RF most likely would produce the greatest tumor heating without significant temperature rise in the normal muscle (refer to Animal Hyperthermia Studies reported below). More extensive dielectric property measurements on a wide variety of normal and neoplastic tissues are needed so that comparisons similar to those above for the rat sarcoma and muscle tissues can be performed.

A large number of in-situ measurements were performed on seven mouse tumor lines and associated normal host tissues over the 10 MHz - 4 GHz frequency range [25,26,28]. The mouse tumor lines measured included three lines of Mammary Adenocarcinoma, Lewis Lung Carcinoma, Melanotic Melanoma B16, Ependymoblastoma and Glioblastoma. Multiple measurements at a single tumor site yielded highly repeatable results which were relatively sensitive, however, to location of the probe on the tumor. For example, measurements performed with the probe in a highly vascularized region of a tumor compared to measurements made with the probe in a poorly vascularized region of the same tumor produced differences of 20% in measured dielectric properties -- a result very similar to that observed in the rat sarcoma measurement on vascularized tumor surface and less vascularized sub-surface tumor (Figure 3). The measured in-vivo dielectric properties of the individual specimens tested within each of the seven mouse tumor lines were averaged (4 to 12 specimens were measured within each line), and then compared to the measured dielectric properties of several normal tissues. The results of these comparisons are presented in Figures 5-8.

The dielectric constant and conductivity of three Mammary Adenocarcinoma lines (Barrett MA, Medecki MA, MA16/C) are compared to similar data from rat muscle and canine fat over the 10 MHz - 4 GHz frequency range in Figure 5. Throughout this frequency range, both the relative dielectric constant and conductivity of all three tumors are significantly higher (100-300%) than that of canine fat. This result indicates that a similar breast tumor under equivalent perfusion conditions would tend to absorb energy at these frequencies more readily than would the surrounding normal, fat-like breast tissue. The figure illustrates the enormous potential of differential hyperthermia induced by EM radiation at these frequencies for the treatment of breast cancer. The fact that the conductivity of mammary tumors is relatively high tends to favor the use of dielectric heating to induce hyperthermia at frequencies in the 0.25-0.4 GHz range for deep tumors and at frequencies of 1.5-2.0 GHz for more superficial ones. For this case, dielectric heating at microwave frequencies would be preferable to resistive heating at very low frequencies, which would heat the normal breast tissue more readily.

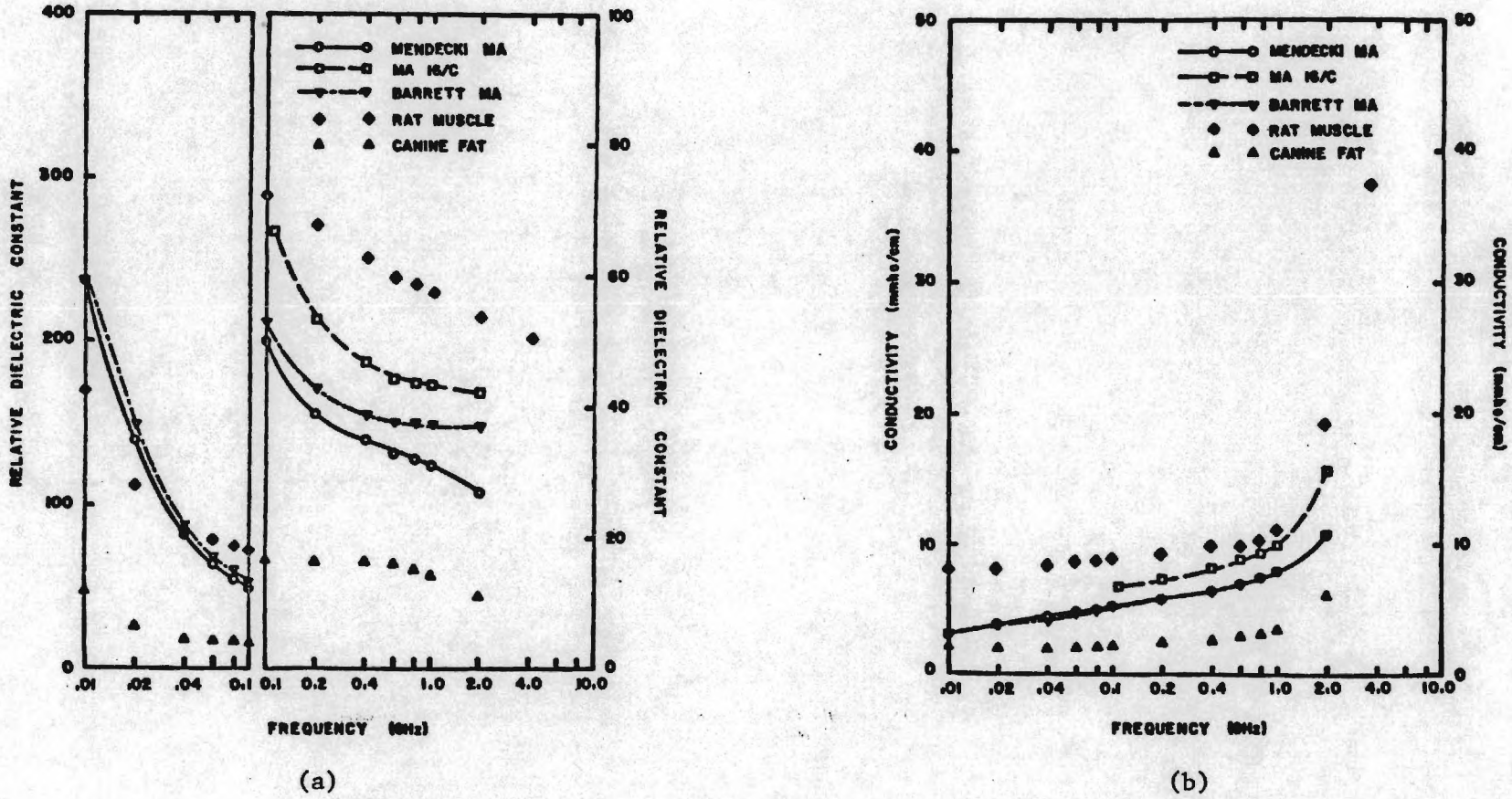


Figure 5. (a) Relative dielectric constant and (b) conductivity of three mouse mammary adenocarcinoma lines, rat muscle, and canine fat.

Figure 6 compares the dielectric properties of Lewis Lung Carcinoma to those of rat muscle and canine fat and muscle and those of an aerated lung model which is mostly air. Throughout the frequency range, the dielectric properties of the dense tumor are more nearly comparable to those of muscle than to those of the aerated lung model or fat. Thus, even deep-seated lung tumors could be differentially heated by EM radiation at a frequency affording reasonable penetration and heating, perhaps over a range of 0.15 GHz to 2 GHz. At these frequencies, the tumor tissue would absorb far more of the microwave energy than the surrounding lung, and could thus be heated differentially and destroyed.

Figure 7 compares Melanotic Melanoma B-16 to normal canine kidney and fat and to rat muscle. Difference between the dielectric properties of the melanoma and the normal tissues are greatest at the lower frequencies, from 10-50 MHz. These are the frequencies at which resistive heating of tissues by induced ionic currents is most effective. Also, tissues with higher resistivity (lower conductivity) tend to absorb more energy during resistive heating than those with higher conductivity. These observations indicate that resistive heating at frequencies below 50 MHz could prove to be an ideal method for inducing differential hyperthermia in the treatment of superficial melanomas, providing that the applicators used to couple energy into the tumor were designed to deposit the energy in a relatively small region in order to avoid excessive heating of subcutaneous fat, which is even lower in conductivity than melanoma tissue.

Figure 8 compares the dielectric properties of two implanted brain tumors (Ependymoblastoma and Glioblastoma) to the properties of normal rat and canine brain tissues. As the data indicate, the conductivity of both tumors from 0.1 -2 GHz is 25-50% higher than that of normal brain tissue. These data point to the use of frequencies in the upper MHz to low GHz range (0.7-1.5 GHz) in inducing differential hyperthermia brain tumor treatment. Applicators at these frequencies would probably be designed to couple radiated energy into the tumor. Higher frequencies could be used for surface tumors, thereby minimizing the possibility of excessive heating of normal brain tissue. For deeper tumors, lower microwave frequencies could be used to obtain maximum penetration without heating the less conductive normal brain tissue.

Preliminary measurements were also made on normal and neoplastic surface tissues in human cancer patients. Some of the results of these measurements appear in Figures 9-11. The average values for multiple measurements of each tumor appear in these figures. Probe contact pressure was found to be a significant factor in these measure-ments. Contact pressure was normalized for each measurement by applying steadily increasing probe pressure until no change occurred in the measured phase angle of the probe's complex reflection coefficient (observed on the network analyzer display) with increasing pressure. The probe pressure was then maintained constant for the duration of the measurement. Using this procedure, very small standard errors were obtained for multiple measurements of the same area (refer to Figures 9-11).

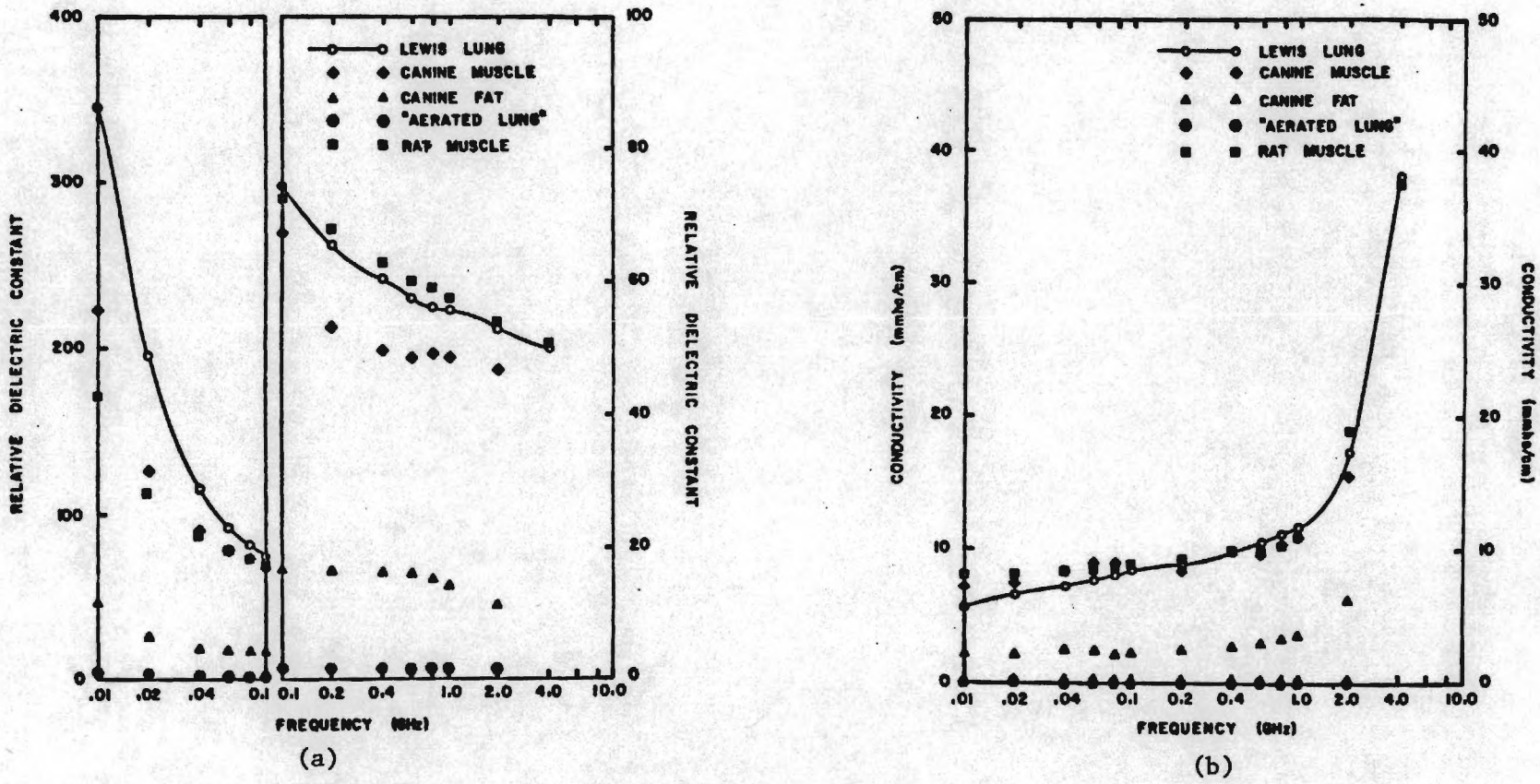


Figure 6. (a) Relative dielectric constant and (b) conductivity of Lewis Lung Carcinoma, canine muscle and fat, rat muscle, and "aerated lung."

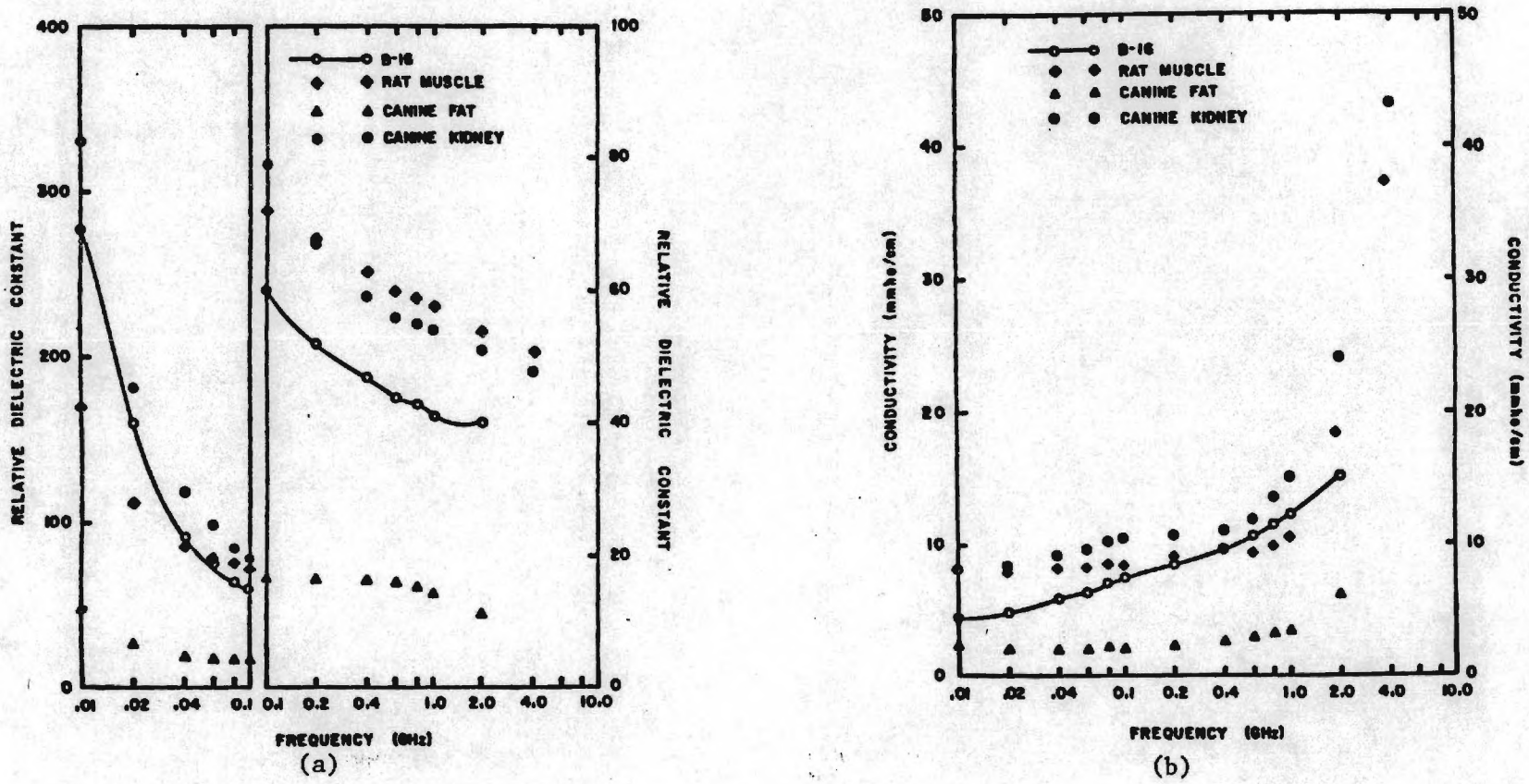


Figure 7. (a) Relative dielectric constant and (b) conductivity of Melanotic Melanoma B-16, rat muscle, canine fat, and canine kidney.

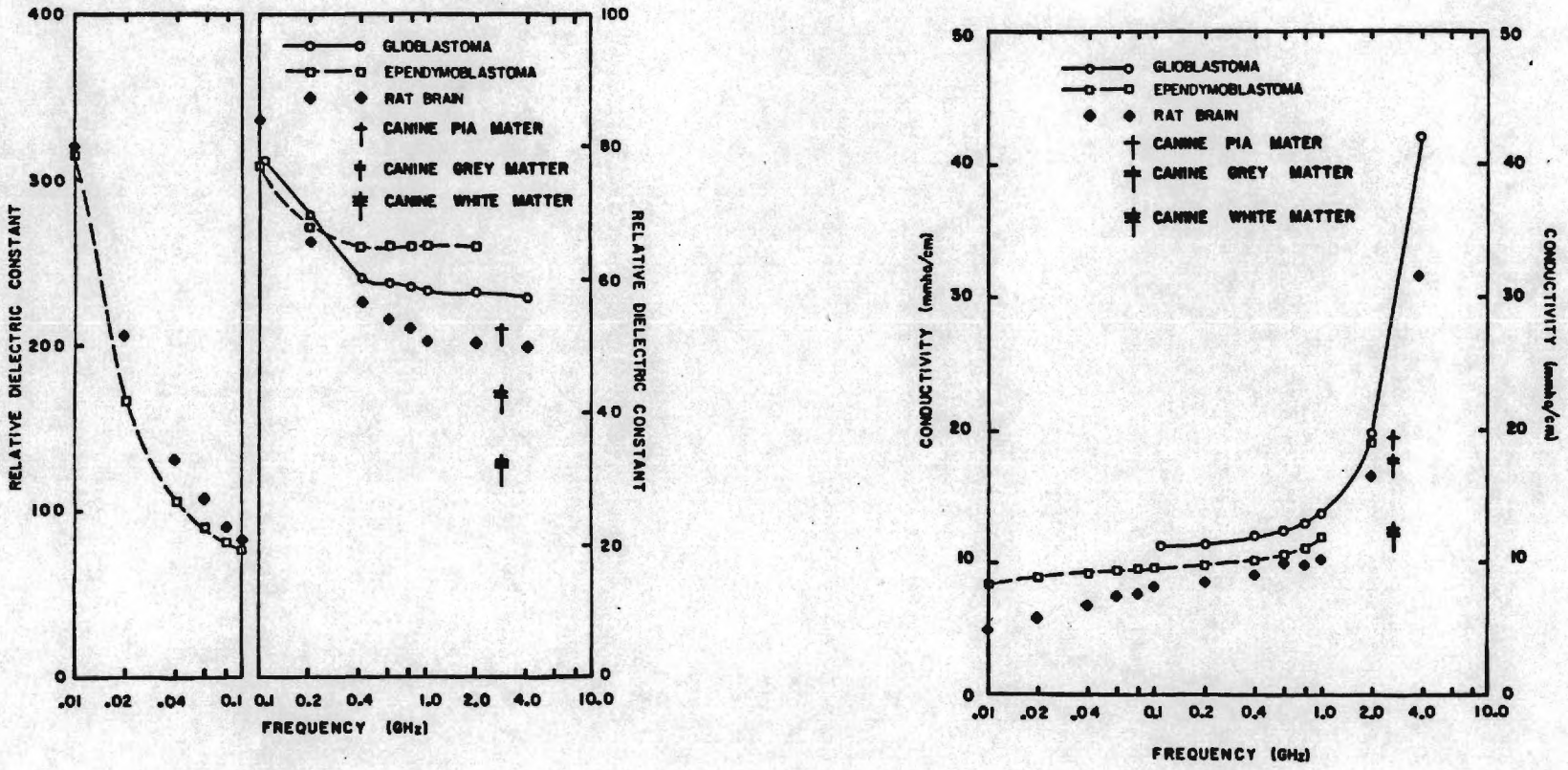


Figure 8. (a) Relative dielectric constant and (b) conductivity of two implanted brain tumors in mice, rat brain, and canine brain.

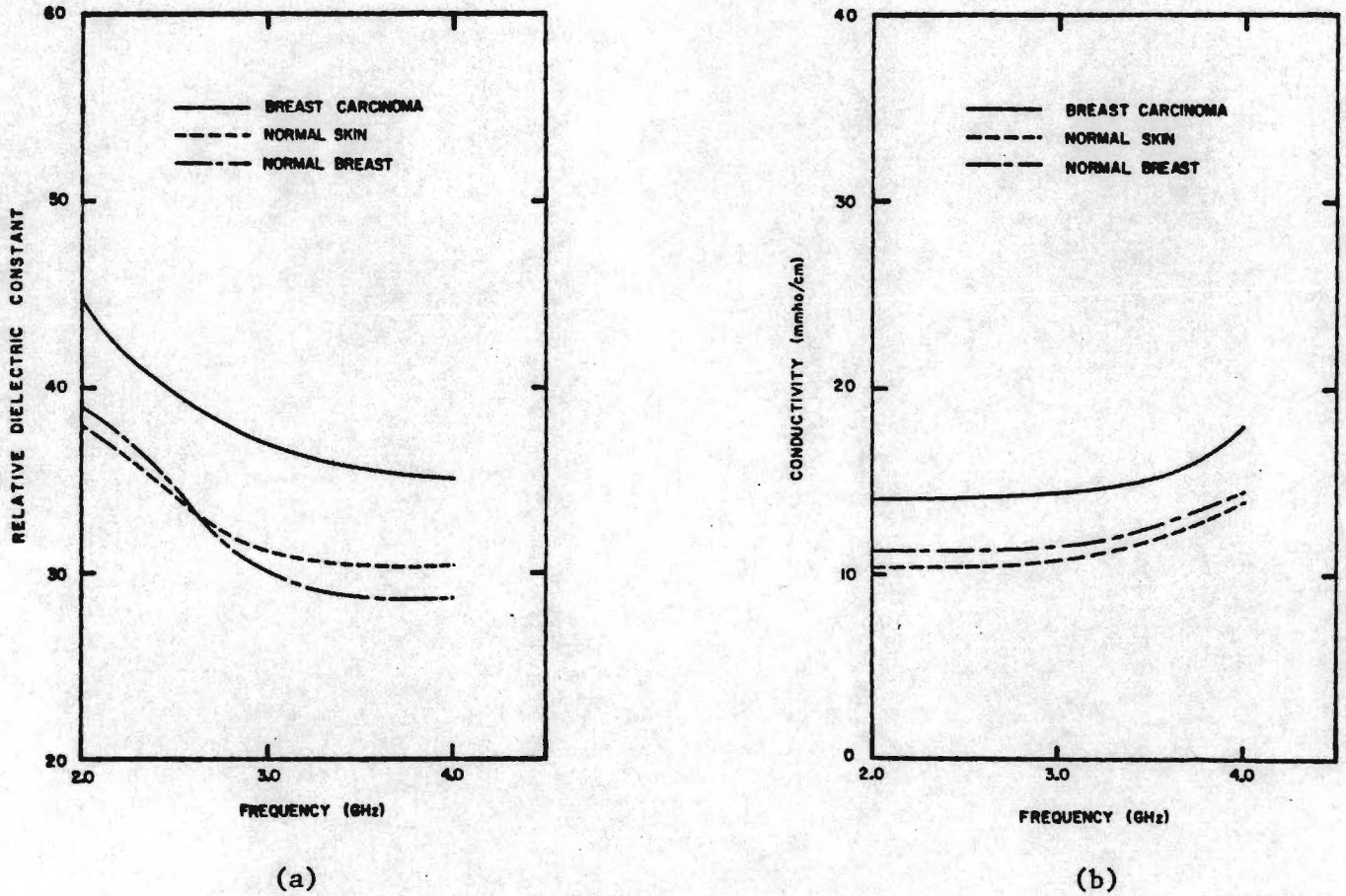


Figure 9. (a) Relative dielectric constand and (b) conductivity of a human mammary carcinoma, normal skin, and normal breast tissue. Maximum SEM for tumor measurements: $K' = \pm 8.47$; $\sigma = \pm 2.61$.

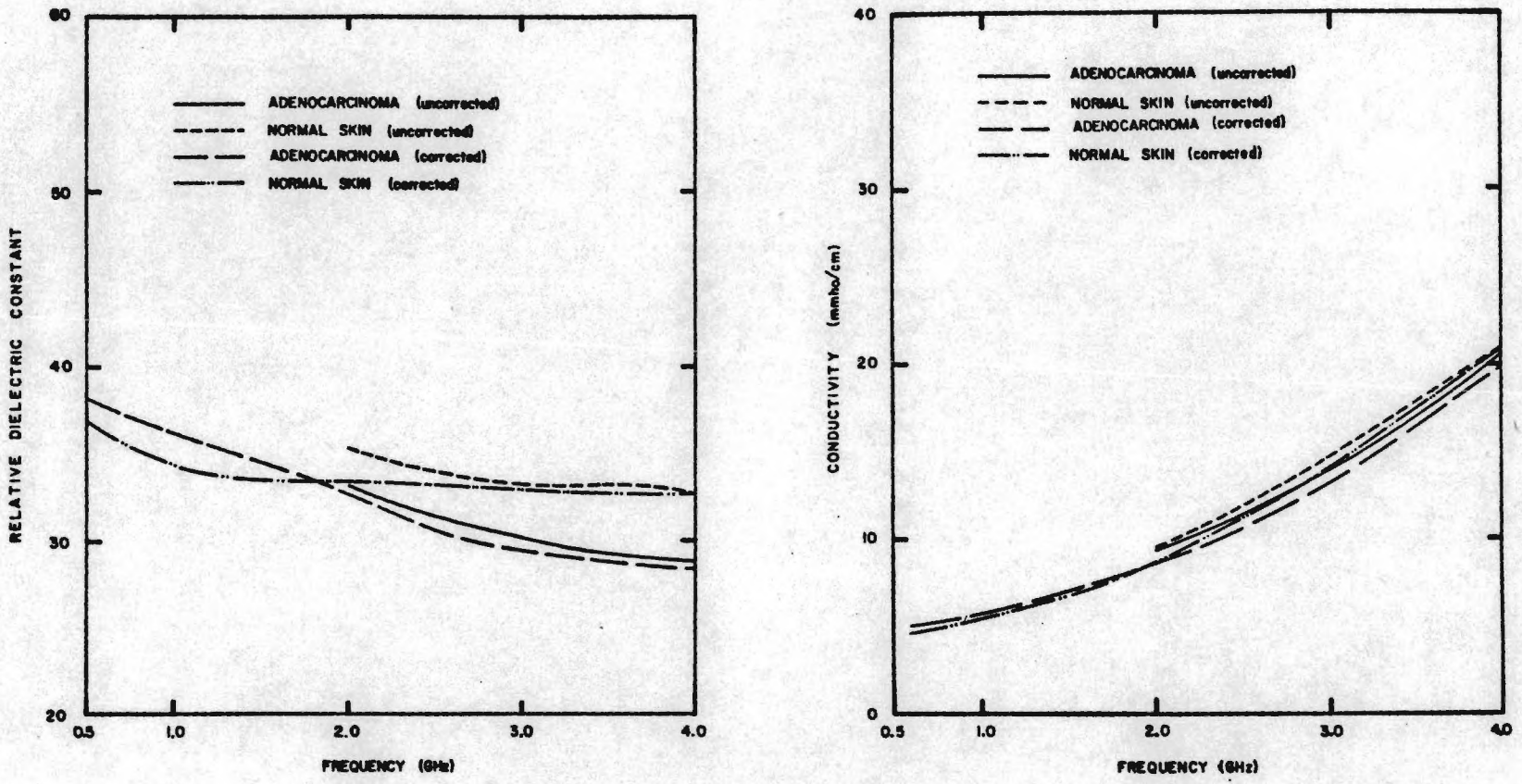


Figure 10. (a) Relative dielectric constant and (b) conductivity of a human adenocarcinoma and normal skin. Maximum SEM for tumor measurements: $K' = \pm 2.70$; $\sigma = \pm 2.39$.

Figure 9 compares the dielectric properties of breast carcinoma tissue to those of normal skin and normal breast tissue. It is worth noting here that the dielectric properties of the human breast carcinoma at these frequencies are similar to those of the mammary adenocarcinomas in experimental animals, and the conductivity data for normal breast tissue more closely approximates that for canine fat (Figure 5). This result lends further credence to the animal model used in the initial dielectric properties studies. These results are preliminary, however, and more information is needed in order to obtain conclusive evidence. Figure 9 also illustrates the elevated conductivity and dielectric constant of breast tumor tissue relative to normal breast tissue. Superficial tumors of the type measured might therefore be successfully treated by microwave radiation-induced hyperthermia at these frequencies.

The dielectric properties of adenocarcinoma in the neck of a patient are compared to those of the normal skin surrounding it in Figure 10. This figure also shows the effects of systemic vector error correction on dielectric property data taken using the probe dielectric measurement technique. As the figure illustrates, the errors are relatively small, yet they could have a significant effect in predicting power absorption in electromagnetically-irradiated tumor tissue. Figure 10 also indicates that inducing differential hyperthermia in this frequency band is plausible only by using radiated energy at frequencies below approximately 1.5 GHz, and even at those frequencies, the conductivity difference between tumor tissue and normal skin would be primarily dependent upon perfusion. It is evident that data are required over a wider frequency band to make an *a priori* determination of a frequency and applicator for use in treating this type of tumor by EM hyperthermia.

Finally, Figure 11 compares the dielectric properties of a superficial melanoma to those of the patient's normal skin. The *in-situ* dielectric properties of this tumor are also similar to those measured for Melanotic Melanoma B-16 in the mouse (Figure 7), although the human tumor has somewhat less dielectric loss. As the figure indicates, both the conductivity and dielectric constant of this tumor are significantly lower than those of the normal skin surrounding it. This would tend to indicate that resistive heating might be successfully employed in treating these tumors, depending upon relative perfusion.

B. Work Performed During Years 03, 04, and 05

During the third through fifth grant years, efforts focused on examining the significance of dielectric property differences during hyperthermia in an animal model system, investigating measurements of tumor dielectric properties through the intact skin, and studying tumor dielectric changes following hyperthermia.

Recent animal studies involving EM-induced hyperthermia have been conducted by several investigators [31-36]. Recent work conducted by Dr. Auda of our group focused on different temperature gradients obtained when using different frequencies in a small animal tumor model. The animal model used

for all experiments consisted of the following: Syngeneic methylcholanthrene induced sarcoma cells to the Fischer rat strain were innoculated into the subcutaneous tissue of the hind limb. After the tumor reached the dimensions required for treatment, the animals were anesthetized, temperature probes were introduced through an 18-gauge needle into the tissues to be studied and hyperthermia was induced by generating an electromagnetic field between two copper contact electrodes placed opposite each other on either side of the anatomical site to be treated. In the first set of experiments, temperature levels within the tumor mass were observed to be higher than the temperature of subcutaneous and muscle tissues that were within the same electromagnetic field (refer to Figures 12 and 13). This finding was in agreement with that of other researchers who had used similar types of tumors [34-37]. In larger tumors, a correlation was observed between the peak temperatures reached during the treatment interval and the amount of absorbed power required. A significant finding in all experiments was that the systemic temperature was not increased by the EM radiation. In different experiments using a fixed frequency of 3.0 MHz and a constant incident power density of 0.30 watts/cm^2, an overall temperature pattern was observed that was similar for tumors of different sizes. A rapid initial increase in temperature was observed, followed by attainment of a steady-state condition and finally, upon termination of the treatment, a rapid decline in temperature to levels lower than those at the start of the treatment. In experiments, temperatures were measured in three different parts of the tumor: the superficial part of the tumor, the core of the tumor, and the deeper aspect of the tumor. Of noteworthy interest was the fact that the temperatures recorded at any one site within the tumor were not statistically significantly different from one point in the tumor to the other, while the temperature of adjacent normal tissues was significantly lower. When larger tumors were treated, temperatures within these tumors were significantly lower than the temperatures obtained in smaller tumors using the same incident power density. This effect was due to the larger tumo volume being heated with the same amount of energy. It was also found that the rate of initial temperature rise was greater for smaller tumors than for large tumors. In all experimental groups, the temperature within the tumor itself when compared to the surrounding non-tumor tissue was higher. Results of heating at each of three different frequencies (3.0 MHz, 13.56 MHz, and 27.22 MHz), where the incident power density was the same at each frequency, were also analyzed (refer to Figure 12). It was determined that frequencies of 3 MHz and 13.56 MHz produced similar heating patterns within the tumor with minimal effect on nearby non-tumor tissues, while the same incident power density at 27.22 MHz temperature levels similar to those obtained with the lower frequencies, the incident power density had to be doubled (Figure 14). However, no selectivity in power absorption by the tumor with respect to normal tissue was obtained with higher power density at 27.22 MHz (Figure 13). That is, the temperature within the tumor was not greater than the temperature in the nearby non-tumor tissues.

The selective heating of neoplastic tissue has also been postulated to be caused by a decreased dispersion of heat by the tumor due to its decreased blood flow. Blood flowing by means of the capillary network in normal tissues

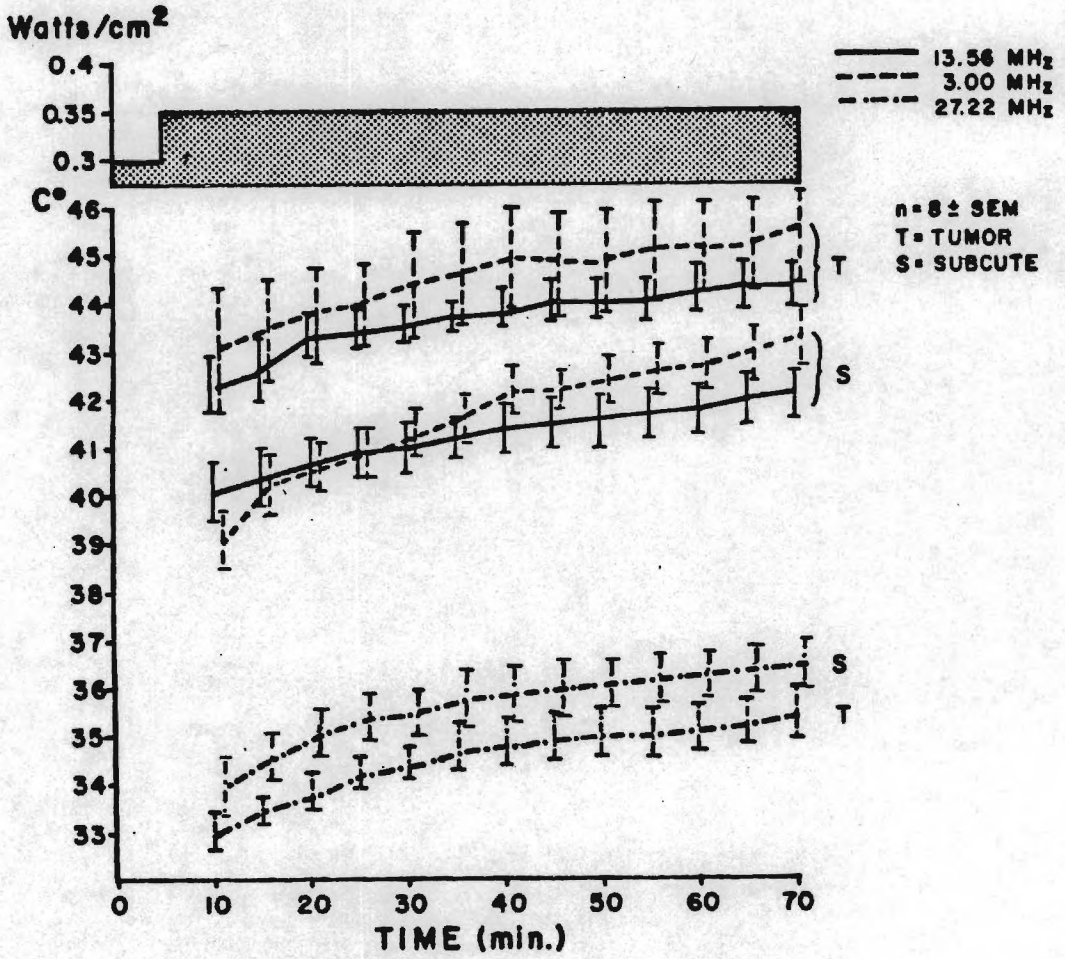


Figure 12. Mean ± SEM of the temperature recordings in the tumor and subcutaneous tissue during the RF treatment interval.

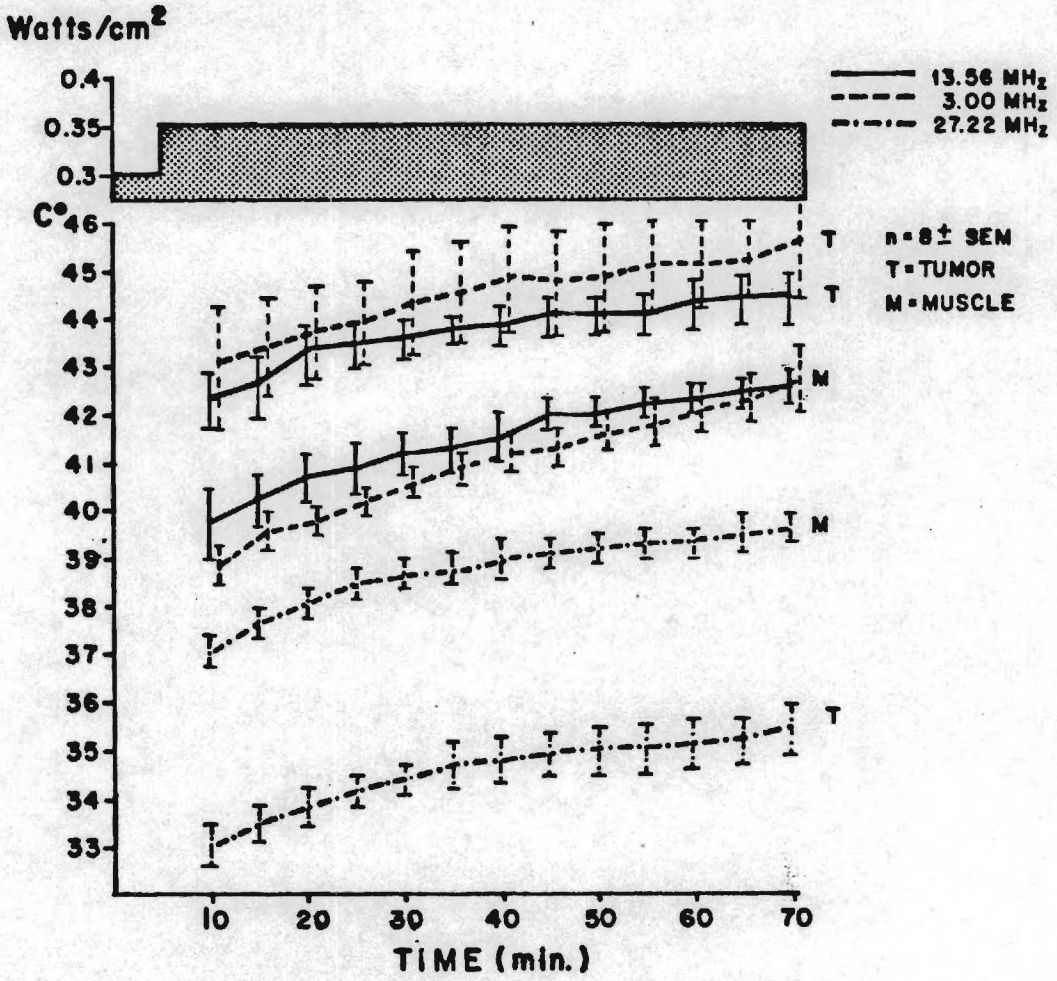


Figure 13. Mean ± SEM of the temperature recordings in the tumor and muscle mass during the RF treatment interval.

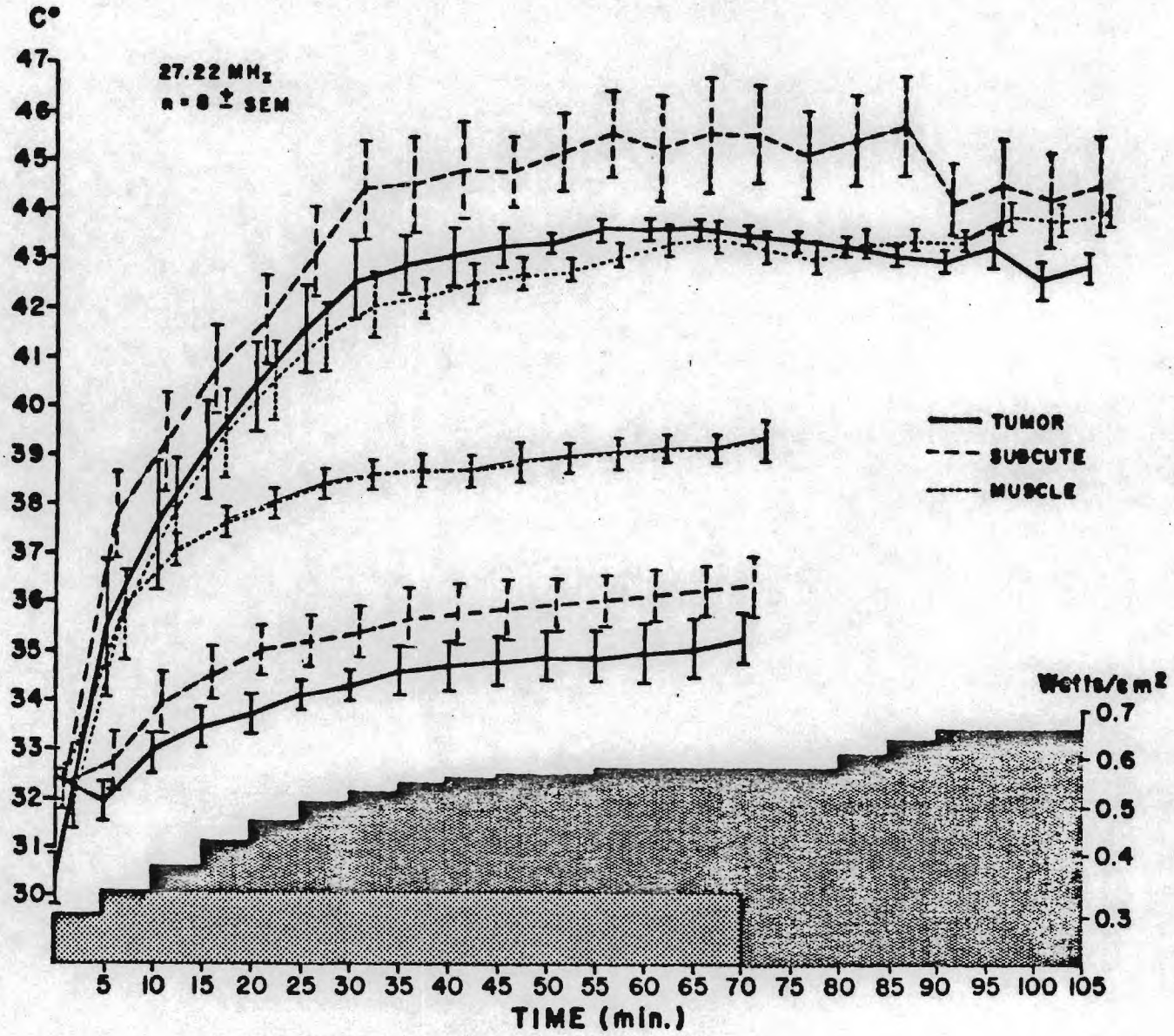


Figure 14. Mean ± SEM of the temperature recordings in the tumor, subcutaneous, and muscle tissue of rats in Groups C and E at a frequency of 27.22 MHz.

dissipates heat through a "radiator" effect. However, some tumors do not possess an ordinate vasculature such as do normal tissues. Casts of human livers with metastases have shown vascular deformities at the site of the lesions [38]. Blood supply was found to be poorer in primary human tumors as well as in experimental tumors in animals compared to the organ in which they were situated, when studied by a quantitative method using radioactive microspheres [39]. A decrease in tumor blood flow by a factor of 20 as compared to normal organs was demonstrated by both a direct and an indirect method in experimental animals [38,39]. Similar results were obtained in rabbits with transplanted V-2 carcinoma when regional tumor blood flow was determined by a krypton-85 clearance technique [40]. While a reduced tumor blood flow could possibly explain the tumor temperature selectivity to both 3 MHz and 13.56 MHz, it certainly does not explain why, when using a different frequency (i.e., 27.22 MHz), comparable results were not obtained. Nor does this explain why, when measuring temperatures in different sites within the same tumor, significantly different temperatures are not obtained from the different parts of the tumor when it is known that these tumors tend to have a varying consistency and morphology at various sites within the tumor (the major necrotic mass is usually located at the core of the tumor itself while in the periphery of the tumor there is usually a more vascularized area in which more heat dissipation, and therefore less heating, would be expected). However, based on the animal in-situ dielectric property measurements performed under this grant, the absorbed power for the resistive heating obtained using contact electrodes at a frequency of 3.0 MHz would be approximately twice as great as the power absorption at 30 MHz [41]. For resistive heating, this difference in power absorption (and resultant tumor heating) is almost entirely due to the difference in conductivity at the two frequencies. As shown in Figure 4, the conductivities of the sarcoma and rat muscle tissue differ by only approximately 10% at 30 MHz, whereas they differ by approximately 40% at 3 MHz, thus explaining the lack of selective tumor heating at 27 MHz. The final point above concerning the fact that the entire tumor seems to heat uniformly, although its morphology is different at various sites within the tumor, is a topic which needs further investigation. It is possible that the temperature was not measured in locations with sufficient morphological differences, or possibly, the tumor dielectric properties may vary as a function of tumor morphology in such a manner as to affect the power absorption and local heating characteristics. Adequate, reliable temperature information can be obtained by using a sufficient number of temperature sensors which are transparent to EM radiation to provide a detailed temperature profile within the tumor during EM hyperthermia treatment. The possibility of dielectric property variations within a tumor can be address by performing in-situ probe measurements at various locations within the tumor to effectively "map" the tumor dielectric characteristics. Our measurements of normal canine brain tissue at various depths (Figure 8) indicate that the dielectric properties change as a function of tissue type and location. Also, the dielectric variations with probe location of the tumor in the mice measurements reported above further indicate that dielectric properties may vary with morphology.

A large number of in-situ dielectric property measurements were

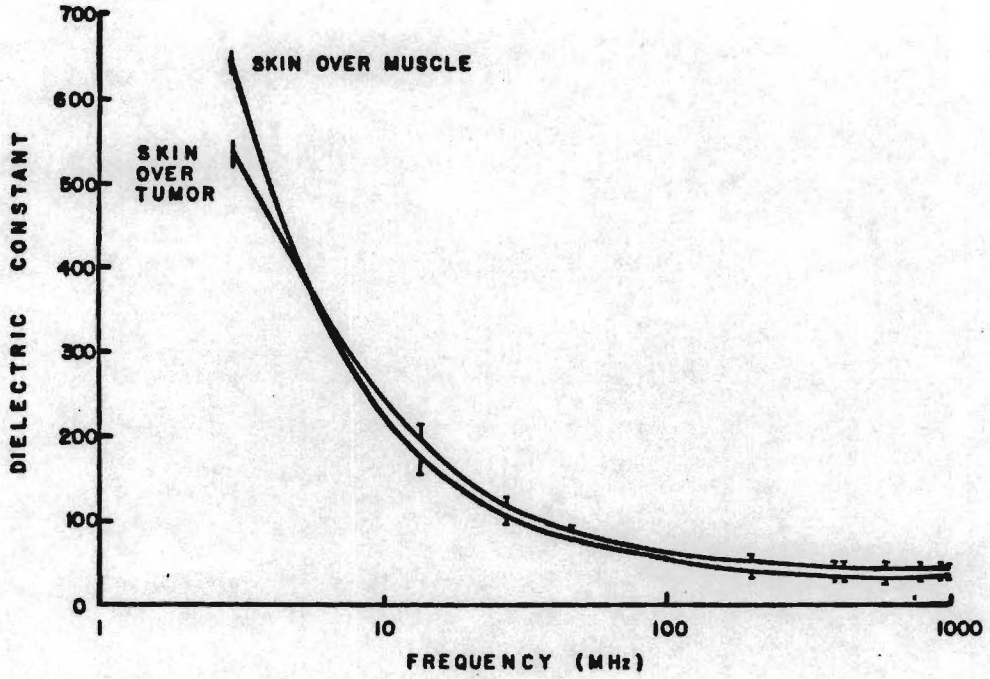
performed on normal tissues and tumors in rats and rabbits. Several groups of in-situ measurements were also performed on human volunteers. In addition, studies of tumor dielectric characteristics preceeding and immediately following hyperthermia were performed primarily to answer the following questions: (1) At what frequencies are differences in the dielectric properties of normal and neoplastic tissues greatest? (2) To what extent are the measured dielectric differences dependent upon the normal host tissues involved? (3) Is it possible to determine differences between the dielectric characteristics of subcutaneous tumors and normal subcutaneous tissue or muscle via noninvasive "through-the-skin" measurements? (4) Do the dielectric characteristics of solid tumors change after EM hyperthermia administration? (5) How do tumor volume and morphology affect the dielectric characteristics of a given tumor type? To varying extents, each of these questions were addressed during the current grant period. Through these efforts, we have learned that fibrous tumors exhibit the greatest dielectric differential with respect to normal muscle, skin, and subcutaneous tissues in the high-frequency (HF) portion of the electromagnetic spectrum. Tumors having liquid necrotic centers exhibited large differences in conductivity and significant differences in dielectric constant when compared to muscle tissue at microwave frequencies. The feasibility of measuring the properties of subcutaneous tumors noninvasively through the intact skin was examined, and consistent differences were observed for "skin-over-tumor" and "skin-over-muscle" measurements. Small intratumor dielectric property differences which appeared to be morphology-dependent were observed in the HF region. Limited experimental studies of the dielectric properties of V-2 carcinoma in the rabbit prior to and following HF hyperthermia indicated consistent increases in electrical conductivity over the 3-30 MHz frequency range after electromagnetic heating.

The results of sarcoma measurements compared to muscle data indicate significant differences in the dielectric properties of the two tissues at frequencies below 40 MHz. For example, at 3 MHz, the relative dielectric constant of the rat muscle is only 52 percent of that of rat tumor, the loss tangent of rat tumor is only 33 percent of that of rat muscle, and the electrical conductivity of rat tumor is only 63 percent of that of rat muscle. At frequencies higher than approximately 50 MHz, the dielectric properties of the rat muscle and tumor tissues are nearly identical. It is apparent that an effort to utilize EM hyperthermia to treat this sarcoma would greatly benefit from knowledge of the dielectric properties of the tumor and normal tissues. The type of EM energy applicator could also be selected with respect to the relationship of the various dielectric properties of the normal and malignant tissues. Because of these differences in the dielectric properties of the two tissues, heating of the sarcoma at frequencies in the 3-20 MHz range would produce the greatest tumor heating without significant temperature rise in the normal muscle.

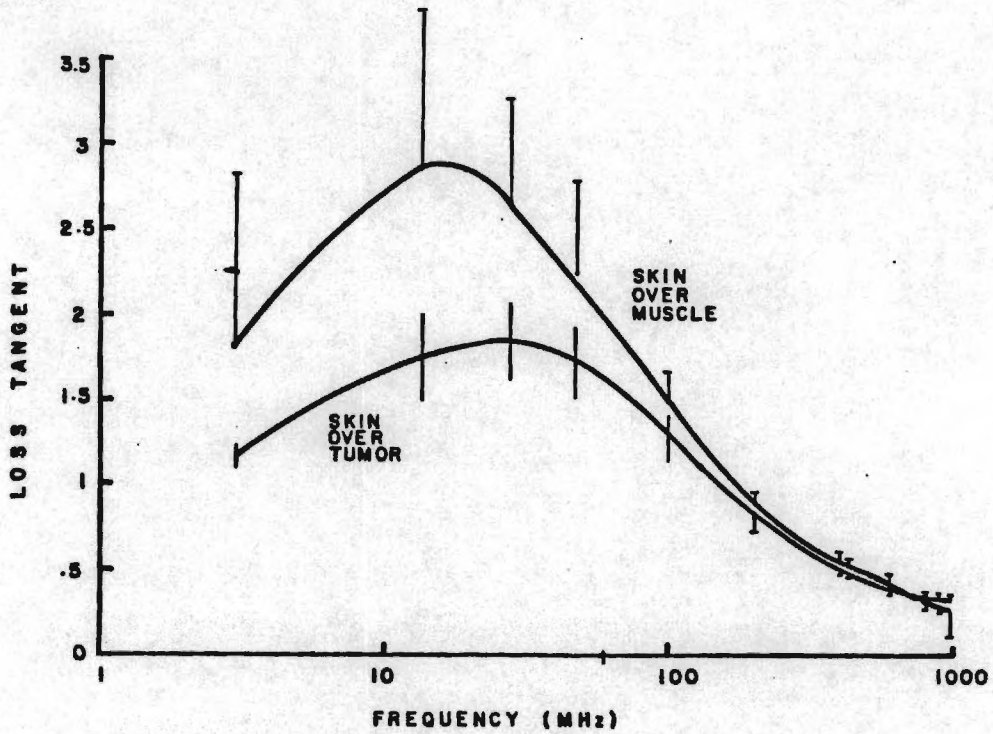
Measurements of muscle and tumor (sarcoma) were also performed noninvasively using a larger diameter probe placed in contact with the intact skin covering the subcutaneous tumor or muscle tissue. From these measurements, it was observed that the differences in measured dielectric constant over the 3-1000 MHz frequency range were not statistically significant. However, significant differences in the conductivity were

repeatedly measured. When measured through the intact skin, the dielectric constant (for both tumor and muscle) was very similar to that of muscle measured directly. The conductivity and loss tangent of tumor and muscle measured through the intact skin were very different; the measured values for each were much closer to the values obtained when measured directly. Thus, it was possible to perform measurements of subcutangeous human tumors noninvasively, without the need for inserting a needle or a surgical incision. Results of measurements of human breast carcinoma are shown in Figure 15 and animal model (rat) results are presented in Figure 16. Although the measured dielectric characteristics of the tumors covered by intact skin are different from results obtained by direct in-vivo probe dielectric measurements, the relative differences between normal tissues and tumors are still evident.

Effects of hyperthermia on the dielectric characteristics of solid tumors were examined in a rabbit V-2 carcinoma tumor model system. In-situ dielectric property measurements in the 3-30 MHz range were performed prior to and following hyperthermia induced by 13.56 MHz radiation. The tumors were heated to 42.5 $\pm$ 0.5^{o}C and adjacent normal tissue maintained at 36-38^{o}C. Twelve animals were included in the study. Data from three were excluded due to technical difficulties. Of the remaining nine animals, four were heated three times each for 30 minutes every day, and five animals were heated three times each for 30 minutes every other day, and five animals were heated twice or once. The protocol is shown in Figure 17. Immediately prior to and following hyperthermia administration, the in-situ tumor dielectric properties were measured. Except for a few cases, the measured changes in dielectric constant were not significant (statistically). Howerver, in nearly every case, a significant increase (3 mmho/cm) in conductivity was measured immediately following heating, but after the tumor temperature had been permitted to return to within 1^{o}C of body temperature. It is speculated that this conductivity increase is due to an increased tumor blood flow. This was measured using thermal dilution methods. Figure 18 presents measured conductivity changes expressed as a percentage of prehyperthermia measured values.

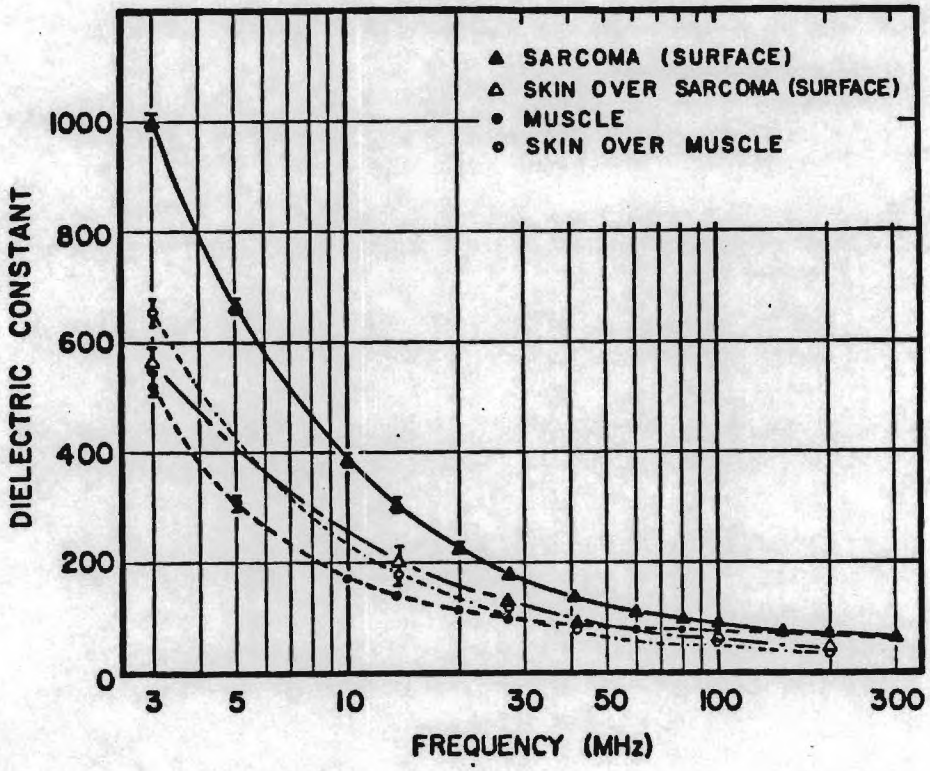


(a)

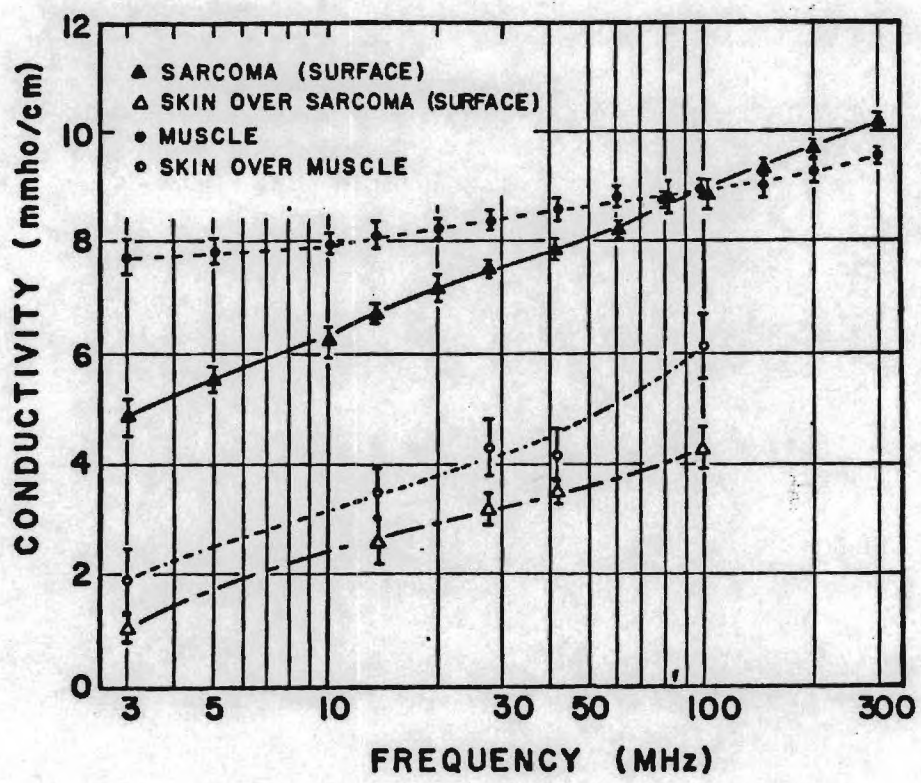


(b)

Figure 15. (a) Dielectric constant and (b) loss tangent of breast carcinoma measured through skin and normal muscle measured through skin using in-vivo probe measurement techniques.



(a)



(b)

Figure 16. (a) Dielectric constant and (b) conductivity from 3-300 MHz of rat sarcoma and muscle tissue measured directly compared to the same properties measured through the skin (hair removed).

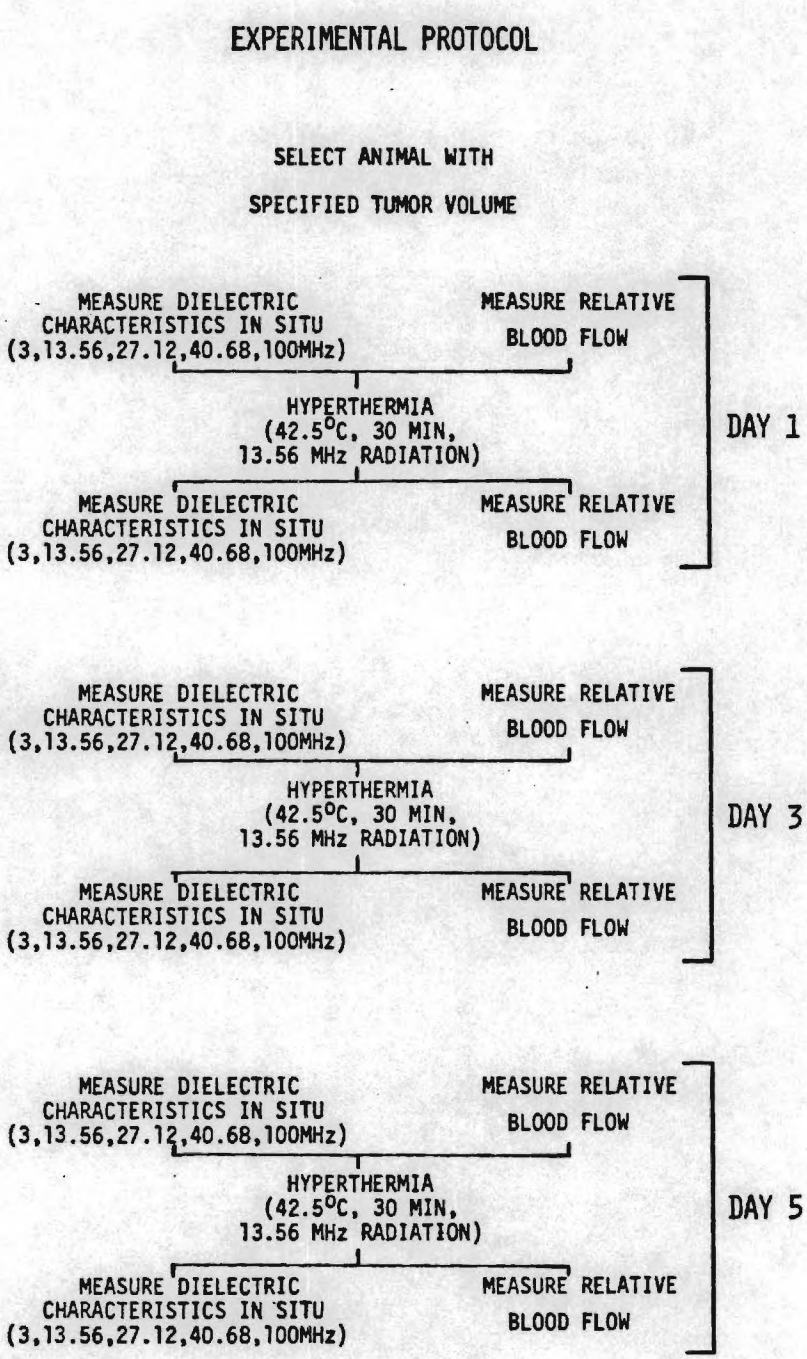


Figure 17. Protocol used for studying dielectric property and blood flow changes produced by EM hyperthermia in rabbit V-2 carcinoma model.

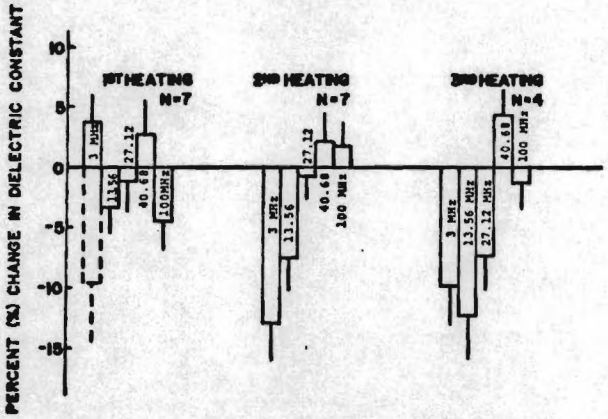
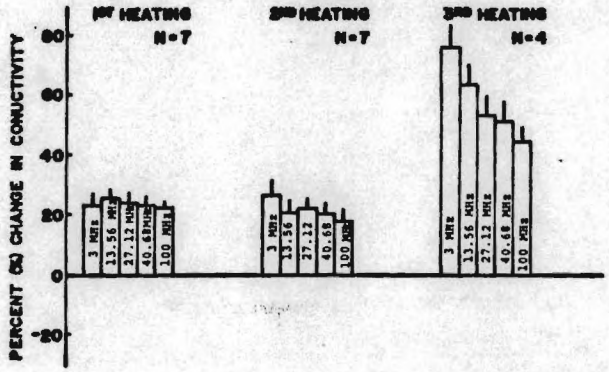


Figure 18. Percent change in dielectric constant of rabbit V-2 carcinoma at five frequencies (3,13.56, 27.12, 40.68, and 100 MHz) following EM-induced hyperthemia (42.5°C).



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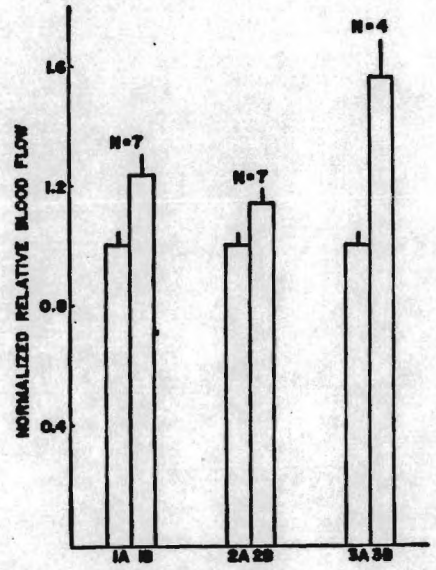

Figure 20. Normalized relative blood flow in rabbit V-2 carcinoma tumor periphery prior to and following hyperthermia induced by EM radiation. Numbers on abseissa indicate 1st, 2nd, or 3rd heating (see Figure 3) and A = before heating, B = after heating.

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